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June 6, 2005

EXPRESS MAIL NO. EV 442379996 US

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Re: Appeal Brief for Patent Application Serial No. 10/059,627 Entitled "Combination of a Growth Factor and a Protease Enzyme"
Our Ref.: CARR-0084 (103216.00252)

Dear Sir:

Enclosed are the following:

1. An Appeal Brief under 37 C.F.R. §41.37 for Patent Application Serial No. 10/059,627; and

2. A check in the amount of $250.00 to cover the filing fee.

If the enclosed check is insufficient or unacceptable for any reason, please charge the remaining fees due to Jackson Walker Deposit Account No. 50-1752. Should you have any questions or any problems processing the enclosed appeal brief and fee, please do not hesitate to notify the undersigned attorney for the applicant.

Thank you for your cooperation and assistance with regard to this matter.

Very truly yours,

T. L Chwang

T. Ling Chwang

TLC/skw
Enclosures

Attorney Docket No.:
CARR-0084 (103216.00252)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Yawei Ni, et al.

Serial No.: 10/059,627

Filed: January 29, 2002

For: **COMBINATION OF A GROWTH FACTOR AND A PROTEASE ENZYME**

Group No.: 1654

Examiner: Michael V. Meller

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

EXPRESS MAIL NO. EV 442379996 US

DATE OF DEPOSIT: June 6, 2005

APPEAL BRIEF UNDER 37 C.F.R. §41.37

This brief is in furtherance of the Notice of Appeal, filed in this case on April 7, 2005.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Carrington Laboratories, Inc., a Texas Corporation, having an address of 2001 Walnut Hill Lane, Irving, Texas 75038.

II. RELATED APPEALS AND INTERFERENCES

With respect to other appeals and interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal, Applicant submits that there are no such appeals or interferences.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

In the application are Claims 1 – 77.

B. Status of All Claims

1. Claims cancelled: NONE

2. Claims withdrawn from consideration but not cancelled: Claims 2, 4, 6, 8 – 12, 16, 18 – 22, and 26 – 77

3. Claims objected to: NONE

4. Claims allowed or confirmed: NONE

5. Claims rejected: Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25

C. Claims on Appeal

The claims on appeal are Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25.

IV. STATUS OF AMENDMENTS

There have been no amendments filed subsequent to the final rejection issued by the Examiner on February 7, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 pertains to a composition comprising a combination formed by mixing two components: (1) a growth factor protein related to epithelial cell functions and (2) an extracellular matrix degrading protease enzyme, as described in the Specification at Page 10, lines 2 – 5. In addition, the composition of Claim 1 comprises a mixture having at least a biologically active fragment of the growth factor protein. As described in the Specification at Page 17, lines 11 – 14 and 16 - 17, the protease enzyme degrades the growth factor to a fragment, but this fragment remains as active as the intact growth factor.

Claim 13 pertains to a composition comprising a mixture formed by mixing two components: (1) a fibroblast growth factor protein and (2) an extracellular matrix degrading protease enzyme. The Specification at Page 10, lines 2 – 5, describes the mixture as it is defined by Claim 1, and Page 10, line 9, specifies that the growth factor protein can be fibroblast growth factor protein. Additionally, the composition of Claim 13 comprises a mixture having at least a biologically active fragment of the fibroblast growth factor protein, as described in the Specification at Page 17, lines 11 – 14 and 16 – 17.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

35 U.S.C. §103(a); All Claims

Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25, stand rejected under 35 U.S.C. §103(a) as being unpatentable over European Patent No. 307847 ("EP 307847"), U.S. Patent No. 4,996,050 ("U.S. '050"), or International Patent Application No. WO 82/03772 ("WO 82/03772"), in view of European Patent No. 619370 ("EP 619370"), U.S. Patent No. 5,589,451 ("U.S. '451"), U.S. Patent No. 5,814,605 (U.S. '605"), International Patent Application No. WO 97/13857 ("WO 97/13857"), or International Patent Application No. WO 98/16243 ("WO 98/16243") ("the Cited References"). The Examiner asserts that the claimed components are used individually in the art for the same purpose and, thus, the combination of the two components is prima facie obvious.

On page 3 of the Office Action dated 02/07/2005, the Examiner has stated:

> "Fact is, the components are used individually in the art for the same purpose. All of the references teach using their respective components (KGF or plasminogen) for the same purpose, namely to treat conditions dealing with repairing of blood vessels and healing of blood related diseases. ...
>
> The law is clear. **All one of ordinary skill in the art has to know is that each of the elements individually are used in the art for the same purpose.** The components are known individually in the art for the same purpose as is of record.
>
> **Thus, to put them together in the same composition is prima facie obvious.** [Emphasis added.]"

The Examiner has also asserted that Applicant has provided no unexpected results.

VII. ARGUMENT

35 U.S.C. §103(a); All Claims

Applicants respectfully assert that Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25 are patentable over the Cited References because the Cited References do not teach a combination of a protein growth factor and a protease enzyme. The combination of a protein growth factor and a protease enzyme is non-obvious because:

(1) there was no motivation nor suggestion in the prior art to combine the two components;

(2) there was no reasonable expectation of success;

(3) common knowledge in the art teaches away from the combination;

(4) the Examiner used impermissible hindsight reasoning to reject the claims; and

(5) the claimed combination demonstrates unexpected results.

A. **No Motivation Nor Suggestion in the Prior Art to Combine the Components**

There was no motivation nor suggestion in the prior art to combine a protein growth factor and a protease enzyme. A protein growth factor is, by definition, a protein. A **protease enzyme, or protease**, is defined as:

> "Any of numerous enzymes that **hydrolyze proteins** and are classified according to the most prominent functional group (as serine or cysteine) at the active site -- called also *proteinase* [Emphasis added]." *See* Merriam-Webster Dictionary 2004.

Another reference defines **protease** as:

> "an enzymatic protein that **breaks down other proteins** [Emphasis added]." *See* Glossary on page 351 of "Understanding DNA and Gene Cloning, A Guide for the Curious," by Karl Drlica, 4th Edition, John Wiley & Sons, Inc. Copyright in 1984, 1997, 2004, pertinent pages are attached as Exhibit A.

Thus, a protease enzyme hydrolyzes, or destroys, proteins.

Applicants assert that **the combination of a first element with a second element, when the second element is commonly known to digest and destroy the first element, is not an obvious combination**. Despite the fact that the two elements individually are used for the same purpose, no one of skill in the art would expect that the combination of two incompatible elements would produce a useful result. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the **prior art also suggests the desirability of the combination**. *See In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Nowhere in the prior art is there a suggestion that it would be desirable to combine (1) a protein, with (2) an enzyme that destroys proteins, to produce a useful composition.

The mere fact that the two components are used for the same general purpose is not enough to render their combination obvious in the absence of some motivation to combine them. The Examiner has asserted that the individual components are both used "with treating blood related conditions, such as wound healing." *See* Final Office Action dated May 4, 2004, Page 3.

Although the two components may be used for treating wounds, they act on totally different aspects of wound healing process. In particular, **growth factors are used to stimulate cell proliferation in a wound, whereas proteases are used to remove or digest debris in a wound as a so-called wound debrider**. Thus, simply because the components are used in treatment of similar conditions, **it does not follow that the components will be compatible in their modes of activity**. **Although pharmaceutical formulations have previously used protease enzymes and growth factor proteins independently, their simultaneous use is counter-intuitive.** The rhetorical question is "Why would one want to combine a protein-degrading enzyme with a protein that can be degraded by the protein-degrading enzyme, unless the purpose is to get a degraded protein?"

Given below is an example involving two house-hold cleaners/disinfectants to demonstrate the fallacy of the Examiner's reasoning that ". . . each of the elements individually are [sic] used in the art for the same purpose. . . to put them together in the same composition is prima facie obvious." *See* page 3 of the Office Action, dated 02/07/2005. In the example given below, both cleaners/disinfectants are used for the very same purpose of cleaning a surface, yet they are **not** be combined and used together.

One house-hold cleaner/disinfectant is Summer Fresh Lysol® brand Disinfectant Cling Toilet Bowl Cleaner. It is used as a disinfectant to kill germs and clean the surface area, such as toilets. This product contains alkyl and other ammonium chlorides as active ingredients.

Another house-hold cleaner/disinfectant is Ultra Clorox® Regular Bleach. It is also used as a disinfectant to kill germs and clean the surface area, such as toilets. In fact, the label gives specific instructions on how to disinfect and sanitize, i.e. clean toilets. This product contains 6% of sodium hypochlorite as the active ingredient.

Thus, according to the Examiner's logic, it is prima facie obvious to put these two disinfectants together in the same composition, because "[t]he law is clear. All one of ordinary skill in the art has to know is that **each of the elements individually are used in the art for the**

same purpose . . . [t]hus **to put them together in the same composition is prima facie obvious** [Emphasis added]." *See* page 3 of the Office Action dated 02/07/2005.

But, that is not the case. As anyone who has ever cleaned a toilet knows, you must never combine a Lysol® brand disinfectant with a Clorox® brand disinfectant. The label on the bottle of a Summer Fresh Lysol® brand Disinfectant Cling Toilet Bowl Cleaner says: "NEVER USE [THIS PRODUCT] WITH CHLORINE BLEACH OR ANY OTHER CHEMICAL PRODUCT."

The main reason for not combining these two disinfectants (**each of them individually is used for the same purpose of cleaning and disinfecting**) is that Lysol® brand toilet bowl disinfectants contain benzyl and alkyl ammonium chlorides, while Clorox® brand disinfectants contain sodium hypochlorite. **The combination of these ingredients doesn't produce an obvious third type of disinfectant, but rather dangerous chemical reactions that are to be avoided by one doing the cleaning**. Thus, it is **not** always obvious to combine two ingredients which act individually for the same purpose. **Their inherent chemical properties may be antagonistic to each other, creating a negative result when combined**.

In addition, simply because the components are used for the same purpose, **it does not follow that the components will be compatible in their modes of operation**. There are many ways to clean and disinfect a toilet bowl, just as there are many ways to promote wound healing. Individually, the chemical effects of benzyl and alkyl ammonium chlorides **OR** the chemical effects of sodium hypochlorite will satisfactorily clean and disinfect a surface. However, their mechanisms of action and their chemical properties are different.

Before obviousness may be established, the Examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles. Logic compels that the suggestion or motivation be accompanied by a general knowledge of the existence of art-recognized techniques for carrying out the proposed invention. *See Ex parte Krantz*, 19 U.S.P.Q.2d 1216, 1218 (B.P.A.I. 1990). Furthermore, the motivation to make a specific invention is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the invention to have, if made. The critical

inquiry is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *See In re Newell*, 891 F.2d 899, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir. 1989). The current application utilizes a unique **combination of a protease enzyme and a growth factor protein** to produce a synergistic effect previously unknown, unanticipated, and contrary to the common wisdom of those of skill in the art. None of the cited references suggests the desirability, or even the feasibility, of combining a protease enzyme and a growth factor protein. Such a combination is completely contrary to sound scientific principles. Lacking motivation to do so, it would not have been obvious to one of skill in the art to combine a protein with its classic antagonist, a protease enzyme. For that reason, the claimed subject matter is non-obvious

B. No Reasonable Expectation of Success

There is no reasonable expectation of success in combining a protein growth factor with a protease enzyme. **Applicant respectfully asserts that no one of skill in the art would have combined (1) a protein-degrading enzyme and (2) a protein with a reasonable expectation of success. The common wisdom is that the protein-degrading enzyme in such a combination will simply degrade the protein, hence rendering the protein ineffective.**

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. *See In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986). Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *See In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Applicant recognizes that the prior art clearly teaches the use of the plasminogen protease enzyme **alone** and the KGF protein **alone**. However, **the prior art cannot be combined to reject the claimed combination of plasminogen and KGF because there is no reasonable expectation of success**. Plasminogen is a protease enzyme which degrades proteins. KGF is a protein. A combination of plasminogen and KGF would, according to expectation, result in the undesirable outcome of plasminogen acting to degrade KGF and destroy its activity. Without an expectation of success, the combination could not have been obvious.

Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *See In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). For anyone of ordinary skill in the art, the consideration to combine two or more agents is driven by the desire for the enhanced effect, either additive or synergistic, and the feasibility to combine them. For example, it would not be advisable to combine an acidic drug with a basic drug as the combination would lead to neutralization or complex formation, thus eliminating the effect of both drugs. In the current application, a protein and a protease enzyme are combined. It is well taught to everyone of skill in the art that a protease is an enzyme that digests, destroys, or breaks down a protein. **There would have been no reasonable expectation of successfully producing an effective composition for treatment of injuries by combining a particular growth factor protein with a particular protease enzyme, based on the knowledge that the components are antagonistic.** Because there was no reasonable expectation of success in combining the claimed components, the claims would not have been obvious.

C. Common Knowledge in the Art Teaches Away from the Combination

Common knowledge in the art teaches away from combining the two claimed components, so the claimed composition is non-obvious. An applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect. *See In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1297, 1365 (Fed. Cir. 1997).

If references taken in combination would produce a "seemingly inoperative device," such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness. *See McGinley v. Franklin Sports Inc.*, 262 F.3d 1339, 60 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 2001). A person of skill in the art would expect that mixing the two components would produce a mixture of an inactive, degraded protein and an active protease enzyme. Such a mixture would be no more useful than a protease enzyme alone. Thus, the "device," being the mixture of the two components, would be inoperative.

By way of example, it is common knowledge that, because of its extremely basic pH, a strongly basic solution is an effective disinfectant. It is also common knowledge that, because of its acidity, a strongly acidic solution is an effective disinfectant. However, it would not be obvious to combine a strongly basic solution and a strongly acidic solution to produce an effective disinfectant because, according to common knowledge in the art, combining an acid and a base results in a neutral (neither basic nor acidic) solution having no disinfecting properties. **Thus, contrary to the Examiner's assertion, it is not always obvious to combine individual components used separately for the same purpose in order to produce a new composition having similar or enhanced activity.** If the ingredients are known to react adversely to each other, like an acid and a base, or a protease enzyme and a protein, it would not have been obvious to combine them. The common wisdom teaches away from their combination. The Examiner's repeated implication that any components under the sun which have the same purpose can necessarily, and obviously, be thrown together to produce a third favorable composition does not take into account the unpredictable and possibly detrimental effects of chemical reactions occurring between the components themselves.

Applicants assert that the combination of a first element with a second element, when the second element is commonly known to **digest and destroy** the first element, is not an obvious combination. Not only is there a complete absence of motivation to make such a combination, but the common knowledge in the art actually **teaches away** from the combination of a protein and a protease enzyme. For this reason, the claims would not have been obvious.

D. Hindsight Reconstruction is Impermissible

The language of 35 U.S.C. §103(a) specifically states that a rejection under this section is only proper when the subject matter of the invention "as a whole" would have been obvious at the time the invention was made to a person of ordinary skill in the art. Thus, an Examiner's use of hindsight reasoning to selectively consider individual components of the invention and the prior art without considering the subject matter "as a whole" is impermissible when making an obviousness determination. *See* MPEP §2145. Inventions are typically combinations of new or

known features. Without consideration of the "as a whole" requirement of §103(a), "an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result – often the very definition of invention." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275, 69 U.S.P.Q.2d 1686, 1690 (Fed. Cir. 2004).

In the current case, the Examiner has used improper hindsight reasoning to conclude that Applicant's combination would have been obvious. In particular, **the Examiner has chosen to selectively fixate on individual aspects of the prior art and apply only these teachings to the Applicant's claimed subject matter**, without considering everything that was known in the art and applying it to the claims as a whole. The Examiner has stated: "The law is clear. All one of ordinary skill in the art has to know is that each of the elements individually are used in the art for the same purpose." *See* Office Action dated 02/07/2005, Page 3. By choosing to rely exclusively on this single teaching, **the Examiner is ignoring all of the prior art teachings which clearly state that protease enzymes are antagonistic to growth factor proteins**. The Examiner has chosen to focus on each component of Applicant's claimed subject matter individually, without consideration for the combination "as a whole" and the effects the combination are expected to have on each component's individual activity. This hindsight analysis of Applicant's invention is impermissible.

It is essential that "the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *See In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q. 2d 1596, 1600 (Fed. Cir.

1988). The Examiner cannot simply consider Applicant's claimed invention, which is an unexpectedly useful combination of two antagonistic components, and conclude that the combination would have been obvious based on the components' characteristics outside of the combination. Rather, the Examiner should have considered whether any person of skill in the art, at the time the invention was made, would have thought it a good idea to combine a protease enzyme and a growth factor protein. The fact that each component individually has been used for different purposes in the general field of treatment of wounds means little in view of the common knowledge of what typically occurs when the components are combined. **Selectively considering particular teachings of the prior art and applying them to each component individually does not comply with the instruction within §103(a) to consider the subject matter "as a whole."** The Examiner has used impermissible hindsight reasoning. The claims, when considered "as a whole," would not have been obvious.

E. The Claimed Combination Demonstrates Unexpected Results

Finally, Applicants' claimed combination of a growth factor protein and a protease enzyme produces unexpected results. Where all elements of an invention were known in the prior art, but not utilized together, if the combination produces unexpected results different from the prior art, the invention may be patentable, particularly where the prior art indicates that the procedure utilized by the patent will be unproductive. *See Milgo Electronics Corp. v. United Telecommunications, Inc.*, 189 U.S.P.Q. 160, 168 (Kan. 1976); *see also W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983). The claimed mixture produces unexpected results different from the prior art because the mixture of a protease enzyme and a protein would be expected to demonstrate a lack of or minimal activity, compared to either component acting alone. A combination of the two components, which might result in any variation of degradation and antagonism, would not be expected to produce a biologically active fragment of protein and a synergistic effect that is greater than the use of either component alone.

Proteins show varying degrees of activity, stability, and degradation in a mixture with protease enzymes. Thus, not only are the components antagonistic to each other, but they are antagonistic in unpredictable and varying degrees. As discussed in the Specification at Page 19, lines 5 – 12, the protease plasmin or plasminogen does not inactivate the growth factor KGF (also known as FGF-7), but does inactivate KGF-2 (also known as FGF-10), another growth factor that can also be used for wound treatment. KGF-2 is very closely related to KGF, yet only KGF-2 is inactivated by plasmin or plasminogen. This fact clearly underscores the subtle difference between these two growth factors and **the non-obviousness of the particular claimed combination between KGF and plasmin or plasminogen**. A combination of plasmin or plasminogen and other growth factors would likely lead to the inactivation of the growth factors. However, the combination of KGF and plasmin or plasminogen by the Applicants produced unexpected results by behaving synergistically in the treatment of wounds. *See* Specification, page 19, lines 13 – 27.

Applicants respectfully submit that Examples 1 – 9 of the Specification clearly outline the unexpected results of the current invention. In particular, Applicants have demonstrated that a combination of a protein growth factor and a protease enzyme produce a composition that synergistically promotes wound healing, despite the fact that the protein growth factor is partially degraded by the enzyme. This is an unexpected result. In order to demonstrate the properties of this unique composition, **Applicants have provided evidence that (1) cleavage of the protein growth factor by the protease enzyme produces an unexpectedly stable fragment of the growth factor, (2) the stable fragment of the growth factor is unexpectedly biologically active, and (3) the combination of the stable fragment of the growth factor and the protease enzyme has an unexpectedly synergistic effect on the promotion of wound healing.**

First, it is an expected result that the combination of a protein growth factor and a protease enzyme will result in unstable fragments of growth factor that are steadily degraded over time in the presence of the enzyme. Applicants have demonstrated that the protein growth factor KGF is cleaved by protease enzymes trypsin, plasmin, and chymotrypsin in Example 1. *See* Specification, Page 24, line 1 to Page 25, line 3. This is not an unexpected result. **The**

unexpected result is that the fragment of KGF remaining after the cleavage by plasmin is stable and not significantly degraded in the presence of the enzyme. In Example 2, Applicants demonstrate the location of the cleavage sites on KGF and show that the KGF fragment (dN23KGF) by plasmin is actually stable, with an intact C-terminus. *See* Specification, Page 25, line 6 to Page 26, line 7. To further demonstrate the unexpected stability of the KGF fragment, Applicants in Examples 3 and 4 increased the protease enzyme concentration and discovered that the degradation of the KGF fragment was not significantly increased. *See* Specification, Page 26, line 8 to Page 28, line 16.

Second, it is expected that any fragments of protein growth factor remaining after contact with a protease enzyme will not be biologically active, or will have diminished biological activity when compared to the intact KGF. Applicants have shown in Example 5 that **the KGF fragment (dN23KGF) which remains after digestion with plasmin is indeed biologically active**. *See* Specification, Page 28, line 17 to Page 29, line 9. This is an unexpected result. An even more unexpected result is Applicant's demonstration in Example 5 that **the KGF fragment (dN23KGF) by plasmin retains as much biological activity as the intact KGF protein**.

Third, it is expected that the combination of a stable, biologically active fragment of growth protein and a protease enzyme would have, at the most, an effectiveness that is equal to the sum of each component's individual effectiveness. However, Applicants have shown in Example 6 that **the two components have a synergistic effect when acting together**. This is an unexpected result. In particular, cells treated with both KGF and plasmin/plasminogen were the only ones to migrate and proliferate in a fibrin gel. *See* Specification, Page 30, lines 6 – 9. Cells treated with KGF and plasminogen showed 20% more fibrin lysis and increased migration. *See* Specification, Page 30, line 26 to Page 31, line 1. **The simultaneous stimulation of cell proliferation by protein growth factors and cell migration by protease enzymes results in an unexpectedly increased amount of proliferation and migration that is greater than the sum of each component acting alone.**

To further demonstrate that the current invention's results are unexpected, Applicants have provided a comparative example in Example 7 and examples showing physiological relevance in Examples 8 and 9. In Example 7, the protein growth factor KGF-2 (or FGF-10) was cleaved by trypsin, plasmin, and chymotrypsin without the production of a stable fragment. All remaining fragments of KGF-2 were steadily degraded in the presence of the protease enzymes. *See* Specification, Page 31, lines 5 – 24. **In light of the protease enzymes' severe degradation of other protein growth factors, the existence of a stable fragment of KGF after protease enzyme digestion is even more unexpected.** In Example 8, Applicants demonstrate that the plasmin contained in wound fluid cleaves KGF in the same manner as in previous examples. *See* Specification, Page 32, line 1 to Page 33, line 2. In Example 9, Applicants demonstrate that native KGF is cleaved to produce exactly the same fragment as the recombinant KGF used in the previous examples.

In light of all of the above, it is clear that the unexpected results shown by Applicant include: (1) a stable growth factor protein fragment is uniquely produced after digestion with protease enzymes; (2) a stable growth factor protein fragment with the same biological activity as the intact growth factor protein is produced after digestion with protease enzymes; and (3) a combination of a stable growth factor protein fragment and the protease enzyme which cleaved the fragment has a synergistic effect on the wound healing capabilities of both ingredients. Because there is no certainty in the art as to which proteins will retain biological activity when mixed with a protease enzyme, nor whether such a mixture will retain any usefulness at all, these unexpected results are significant.

The current claims pertain to a mixture of a protein and a protease enzyme which contains at least a biologically active fragment of protein, and which produces unexpected results and a synergistic utility that is greater than the use of a protease enzyme or a protein alone. *See* Specification at Page 19, lines 13 – 27. This unexpectedly useful mixture of components is not obvious.

In conclusion, Applicants respectfully assert that Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25 are patentable and non-obvious in view of the Cited References. The Examiner **cannot** point to a single reference describing the combination of a protein growth factor and a protease enzyme and has not provided sufficient evidence to demonstrate why such a combination is obvious. The combination of a protein growth factor and a protease enzyme would not have been obvious because (1) there was no motivation nor suggestion in the prior art to combine the two components, (2) there was no reasonable expectation of success, (3) common knowledge in the art teaches away from the combination, and (4) the claimed combination demonstrates unexpected results.

Applicants respectfully assert that the Examiner has not made a prima facie showing of obviousness, and in the alternative, that Applicant has rebutted the Examiner's prima facie showing. Applicants respectfully request that Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25 be allowed.

VIII. CLAIMS APPENDIX

The text of the claims involved in the appeal are:

1. A composition comprising:

a mixture formed by mixing ingredients comprising a growth factor protein related to epithelial cell function and an extracellular matrix degrading protease enzyme, wherein the mixture comprises at least a biologically active fragment of the growth factor protein.

3. The composition of claim 1, wherein the growth factor related to epithelial cell function comprises keratinocyte growth factor ("KGF") or functional biological equivalent thereof.

5. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent thereof.

7. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

13. A composition comprising:

a mixture formed by mixing ingredients comprising a fibroblast growth factor protein and an extracellular matrix-degrading protease enzyme, wherein the mixture comprises at least a biologically active fragment of the fibroblast growth factor protein.

14. The composition of claim 13, wherein the fibroblast growth factor protein comprises keratinocyte growth factor ("KGF") or functional biological equivalent thereof.

15. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent thereof.

17. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

23. The composition of claim 13, wherein the fibroblast growth factor protein has a concentration of from 0.00001% [w/v] to 0.1% [w/v], and the extracellular matrix-degrading protease enzyme has a concentration of from 0.0001 [w/v] to 1% [w/v].

24. The composition of claim 13 further comprising a carrier.

25. The composition of claim 24, wherein the carrier comprises a buffer, a saline solution, a thickener, an emulsion, or an ointment.

IX. EVIDENCE APPENDIX

Exhibit A, which is attached, is submitted in conjunction with this appeal brief.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings pertaining to this appeal.

Respectfully submitted,

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June 6, 2005
Date

EXHIBIT A

Understanding DNA and Gene Cloning

A GUIDE FOR THE CURIOUS

Fourth Edition

KARL DRLICA

Public Health Research Institute
225 Warren Street
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polarity directionality, having a left and a right end.
polyadenylated a property of eukaryotic mRNA consisting of a stretch of adenylates at the 3′ end of the RNA.
polyclonal derived from a variety of cell lines; generally refers to a population of antibodies generated by cells that each produce a slightly different antibody molecule.
polymerase chain reaction (PCR) a test tube reaction in which a specific region of DNA is amplified many times by repeated synthesis of DNA using DNA polymerase and specific primers to define the ends of the amplified region. (Figure 8-5)
polyprotein a long protein that is cleaved into several smaller proteins. The smaller proteins are thought to be the functional forms.
precipitate molecules that are clumped together so that they fail to pass through a filter. Precipitates are large aggregates that settle out of solution rapidly, much like silt out of river water. (Figure 3-8)
prenatal before birth.
primer a piece of DNA or RNA that provides an end to which DNA polymerase can add nucleotides. (Figures 3-8, 8-5)
probe a DNA or RNA molecule, often radioactive, that is used to locate a complementary RNA or DNA by hybridizing to it. Often a probe is used to identify bacterial colonies that contain cloned genes and to detect specific nucleic acids following separation by gel electrophoresis. (Figure 8-2)
product the new molecules produced by a chemical reaction.
progenitor a originator of a line of descent.
progeny offspring.
programmed cell death cell suicide that arises from the action of proteins that have evolved for self-destruction, apoptosis.
prokaryote an organism lacking a true nucleus or other organelles.
promoter a short nucleotide sequence on DNA where RNA polymerase binds and begins transcription. (Figure 4-6)
protease an enzymatic protein that breaks down other proteins.
proteome the amino acid sequences for all proteins encoded by the genome of an organism.
protein a class of long, chainlike molecules often containing hundreds of links called amino acids. Twenty different types of amino acid are used to make proteins. The thousands of different proteins serve many functions in the cell. As enzymes, they control the rate of chemical reactions, and as structural elements they provide the cell with its shape. Proteins are also involved in cell movement and in the formation of cell walls, membranes, and protective shells. Some proteins also help package DNA molecules into chromosomes. (Figure 1-5)